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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,784	12/13/2004	Gideon Gross	GROSS32	4624

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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,784	GROSS ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,11-44,47-53,58 and 59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,11-44,47-53,58 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20070912*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Memo by Dr. Amy Patterson of the Department of Health and Human Services dated January 14, 2003 (pp. 1-3).

DETAILED ACTION

1. Inasmuch as the Office action mailed November 12, 2009, has been vacated this Office action addresses the amendment filed April 25, 2009.

2. Receipt of the amendment filed April 25, 2009, is acknowledged and has been entered. Claims 1, 3, 5, 24, 25, 32, 34, 38, 39, 41-44, 47-52 have been amended. Claims 58 and 59 (renumbered 56 and 57, respectively) have been added.

3. Claims 1, 3, 5, 11-44, 47-53, 56, and 57[1] are pending in the application and are currently under prosecution.

Information Disclosure Statement

4. The information disclosure filed September 12, 2007, has been considered in part. An initialed copy is enclosed.

Non-patent literature documents cited at page 2 have not been considered because the citations are incomplete inasmuch as the titles of the journals have been omitted. Due to the omission the documents are not cited in a manner that satisfies the requirements set forth under 37 C.F.R. § 1.98.

Priority

5. Applicant's claim under 35 U.S.C. §§ 119(e) and/or 120, 121, or 365(c) for benefit of the earlier filing date of PCT/IL03/00501, filed June 12, 2003, which claims benefit of Provisional Application No. 60/388,273, filed June 12, 2002, is acknowledged.

However, claims 1, 3, 5, 11-44, 47-53, 56, and 57 do not properly benefit under §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). See M.P.E.P. § 201.11.

Then, apart from this issue, it is further noted that many of the claims do not properly benefit from the earlier filing date of Provisional Application No. 60/388,273 since that application fails to provide written support for the language of the claims. Without limitation, but as an example, it is noted that claim 1, for example, is drawn to a polynucleotide encoding a fusion polypeptide comprising an antigenic peptide from a pathogen, which is either fungal or parasitic in origin; yet, the provisional application does not appear to provide support for such a claim. As another example, claim 1, for example, is drawn to a polynucleotide encoding a fusion polypeptide comprising an the full or partial transmembrane and/or cytoplasmic domains of CD40; yet, it appears that the provisional application does not disclose such a fusion polypeptide and thus fails to provide written support for such a claim.

Accordingly, the effective filing date of the claims is deemed the filing date of international application PCT/IL03/00501, namely June 12, 2003.

Grounds of Objection and Rejection Withdrawn

6. The grounds of objection and rejection set forth in the previous Office action mailed June 29, 2007, have been withdrawn in favor of the new grounds of objection or rejection set forth below in this Office action.

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[1] Claims numbered 58 and 59 have been renumbered 56 and 57 since the Office communications mailed

Response to Arguments

7. Applicant's arguments with respect the grounds of rejection set forth in the previous Office action mailed June 29, 2007, have been considered but are moot in view of the new grounds of rejection.

Grounds of Objection

Specification

8. The specification is objected to because the claims are directed to a plurality of tumor-associated antigens (TAA), which the specification expressly discloses includes "any TAA peptide known or to be discovered in the future as periodically published in Cancer Immunity, a Journal of the Academy of Cancer Immunology, at the website http://www.cancerimmunity.org/peptidedatabase/Tcellepitopes.htm" (paragraph [0079] of the published application[2]).

Although there is written support for the language of the claims in the specification at, e.g., paragraph [0050] of the published application, there is no incorporation by reference statement in the disclosure that properly incorporates by reference the disclosures of any publications in *Cancer Immunity*, which describe the members of the claimed genus of TAAs.

Nevertheless, Applicant is duly reminded that M.P.E.P. § 608.01(p) does not provide for the incorporation by reference of essential material by reference to non-patent publications. Moreover, § 608.01(p) does not provide for incorporation of any information, essential or not, by reference to the contents of websites[3].

"Essential material" is defined as "that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112)".

Information pertaining to the identity, structure, and/or function of the TAA by the referenced journal is essential information because it is necessary to adequately

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November 29, 2007, February 7, 2008, April 9, 2008, and April 6, 2009, have been vacated.
[2] U.S. Patent Application Publication No. 2006/0003315-A1.
[3] Although Applicant amended paragraph [0079]

describe the subject matter to which the claims are directed with the requisite clarity and particularity to satisfy the requirements set forth under 35 U.S.C. § 112, first paragraph.

Thus, if Applicant intends that the information periodically published in *Cancer Immunity, a Journal of the Academy of Cancer Immunology,* at the website http://www.cancerimmunity.org/peptidedatabase/Tcellepitopes.htm be relied upon to resolve issues under 35 U.S.C. § 112, first paragraph, which were raised in the preceding Office action, that information **must** be incorporated into the specification of this application (*which of course seems an impossibility since it necessarily includes information disclosed by future publications in the journal*). Barring the seeming impossibility of incorporating the material incorporated by reference to the journal, Applicant would be required to amend the specification to include the material incorporated by reference; and then too the amendment must be accompanied by an affidavit or declaration executed by Applicant, or a practitioner representing Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim Objections

9. Claims 1, 11, 32, 38, 39, 47, 48, 56, and 57 are objected to because of the repeated use of the terms "carboxyl terminal" and "amino terminal" instead of "carboxyl terminus" and "amino terminus" to apparently denote the termini of different portions of the components of the fusion polypeptide to which the claims are directed.

Appropriate correction of the apparent misspelling or misuse of the terms is required.

10. Claim 16 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

A proper dependent claim must further limit each and every embodiment of the preceding claim.

Claim 16 is drawn to the polynucleotide of claim 15, wherein, e.g., the antigenic peptide is a peptide having an amino acid sequence derived from alpha-fetoprotein (AFP); but according to claim 15, the tumor-associated antigen (TAA) is not necessarily AFP but might instead by some other TAA (e.g., BAGE, CEA, or MART-1) and if the antigenic peptide is a fragment of AFP the TAA is AFP (not BAGE or any other TAA). As that is the case, claim 16 does not properly further limit the subject matter encompassed by claim 15 to the extent that the latter claim is directed to a polynucleotide encoding a fusion polypeptide comprising an antigenic peptide that is a TAA, wherein that TAA is an antigen that is structurally and functionally different from the antigen from which the antigenic peptide is derived.

It is suggested that this issue might be best remedied by amending claim 16 to depend from claim 14, as opposed to claim 15, since it appears that all of the antigenic peptides recited by claim 16 are derived from tumor-associated antigens (TAAs).

11. Claim 17 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 17 depends from claim 14, which in turn depends from claim 12; yet, the limitation recited by both claims 12 and 17 is the same. Accordingly, claim 17 does not further limit the preceding claims.

12. Claim 20 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 20 depends from claim 14, which in turn depends from claim 12. According to claim 12, the at least one antigenic peptide is at least one antigenic

determinant of one sole antigen. As such, the at least one antigen peptide, as in accordance with claim 20, cannot also be at least one antigenic determinant of each of at least two different antigens. Accordingly, claim 20 does not properly further limit the preceding claims.

13. Claim 35 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

A proper dependent claim must further limit each and every embodiment of the preceding claim.

Claim 35 should be amended to depend from claim 32, as opposed to claim 34, since if the antigenic peptide is at least one peptide derived from at least one TAA it is *not* a peptide comprising a MHC class I epitope of an antigen from a pathogen or at least one idiotypic peptide (rather it is a peptide comprising a MHC class I epitope of a TAA).

14. Claim 36 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

A proper dependent claim must further limit each and every embodiment of the preceding claim.

Claim 36 should be amended to depend from claim 32, as opposed to claim 34, since if the antigenic peptide is at least one peptide derived from an antigen from a pathogen it is *not* a peptide comprising a MHC class I epitope of an antigen from a TAA or at least one idiotypic peptide (rather it is a peptide comprising a MHC class I epitope of an antigen from a pathogen).

15. The claims (e.g., claim 1) are objected to because of the use of the term "sequence", apparently with intent to denote a peptide or polypeptide. Claim 1, for example, recites the term “a sequence” that can exert the required anchoring function consisting of the full or partial transmembrane and/or cytoplasmic domain of a molecule recited by the claim. However, a sequence is merely information descriptive of the serial arrangement of individual constituents or units (e.g., the amino acid sequence of a protein defines the order of the amino acids that form the protein); it is not a material of which the claimed fusion polypeptide may be comprised.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

16. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

17. Claims 1, 3, 5, 11-44, 47-53, 56, and 57 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The considerations that are made in determining whether a claimed invention is supported by either a specific and substantial asserted utility or a well-established utility are outlined by the published Utility Examination Guidelines (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: http://www.gpoaccess.gov/.

Briefly, a “specific and substantial” asserted utility is an asserted utility that is specific to the particular nature and substance of the claimed subject matter, and which would be immediately available for application in a “real-world” context by virtue of the existing information disclosed in the specification and/or on the basis of knowledge imparted by the prior art, such that its use would not require or constitute carrying out further research to identify or reasonably confirm its usefulness in this context. A “well-established” utility is a credible, specific, and substantial utility, which is well known,

immediately apparent, and implied by the specification, and based on the disclosure of the properties of a material or subject matter, either alone or taken with the knowledge of one skilled in the art.

Claims 1, 3, 5, 11-44, 47-53, 56, and 57 are drawn to a nucleic acid molecule, a vector comprising said nucleic acid molecule, a cell comprising said vector, a vaccine comprising said nucleic acid molecule, vector, or cell, and a method of immunizing a mammal against a tumor-associated antigen comprising the step of immunizing the mammal with the vaccine.

Each of the claimed inventions is disclosed as useful to prevent or treat cancer or infectious diseases in a mammal; see, e.g., the abstract and paragraph [0111] of the published application.

Yet, to employ the claimed inventions in the prevention or treatment of cancer and any of a plurality of infectious diseases, as is the asserted utility of the claimed invention, would clearly require further research, which should be regarded as constituting part of the inventive process.

Moreover, the existing information disclosed by Applicants' application would merely provide the artisan with an invitation to perform such investigations, which might ultimately lead to a derivation of a specific benefit, or which might not; and in either case, an immediate benefit could not be derived from the use of the claimed invention because the existing information is insufficient to enable the artisan to use the claimed polynucleotide in the manner asserted to provide an immediate benefit. Although the disclosure of the claimed inventions might tomorrow command the grateful attention of the public, the Court has decided:

> [A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

Brenner, Comr. Pats. v. Manson, 148 U.S.P.Q. 689 at 696 (US SupCt, 1966).

So, as further explained in the paragraphs that follow, because the specification does not disclose a currently available, "real world" use for the claimed inventions, the requirements set forth under 35 U.S.C. § 101 have not been met.

The assertion that the claimed inventions can be used to prevent or treat any of a plurality of etiologically and pathologically disparate "infectious diseases" lacks specificity because any benefit that might be derived by the public for a grant of a patent monopoly of the existing information disclosed by Applicants' application is not specific to the substance and nature of the claimed inventions, which notably need not comprise or utilize an antigen associated with the infectious disease, per se, but might instead comprise or utilize, for example, an unrelated tumor-associated antigen. By the same token, the assertion that the claimed inventions can be used to prevent or treat any of a plurality of etiologically and pathologically disparate types of cancer lacks specificity, because any benefit that might be derived by the public for a grant of a patent monopoly of the existing information disclosed by Applicants' application is not specific to the substance and nature of the claimed inventions, which notably need not comprise or utilize an antigen associated with the specific type of cancer to be prevented or treated and might instead comprise or utilize, for example, an unrelated antigen associated with a bacterium or fungus[4].

Consequently, although Applicant has asserted that the claimed inventions can be used to prevent or treat cancer or infectious disease, given only the benefit of the existing disclosure in this application, it is apparent that the claimed invention cannot be regarded as practically useful in the "real-world" setting of the clinic or hospital since, for example, a vaccine comprising a fusion polypeptide comprising an antigen associated with a bacterium is not reasonably expected to stimulate an immune response in a mammal that is effective to prevent or treat cancer in the mammal. Not dissimilarly, a vaccine comprising a fusion polypeptide comprising an antigen associated with a certain type of cancer would not be expected to stimulate immunity in a mammal that is effective to prevent or treat an infectious disease, such as tuberculosis, in the mammal.

Thus, it is submitted that the assertion that the claimed inventions are useful in some abstract capacity to prevent or treat some unspecified type of cancer or infectious

[4] See, e.g., claims 43 and 44, which are expressly directed to cellular vaccines for prevention or treatment of cancer, wherein the antigen is bacterial, viral, fungal or of parasitic origin, or cellular vaccines for

disease, where the claimed product would ordinarily not be considered so useful, lacks the necessary specificity and substantiality of an asserted utility in the chemical arts that might otherwise fulfill the requirements of 35 USC § 101. Again, this is because any benefit that might be derived by the public for a grant of a patent monopoly of the existing information disclosed by this application could not be derived immediately and directly therefrom or without need to first complete the inventive process by performing additional experimentation to identify which, if any of the claimed products might in fact be used to prevent or treat any given type of cancer or infectious disease.

Applicant is therefore reminded that to fulfill the requirements of 35 USC § 101, the skilled artisan must be able to use a claimed invention in the manner asserted by Applicants' to provide some immediate benefit to the public. See *Nelson v. Bowler and Crossley*, 206 USPQ 881 (CCPA, 1980).

Then, for sake of simplifying the very broad and extensive issues related to the purported utility of the claimed inventions, most of the remainder of this discussion will focus on the assertion that the claimed inventions are useful to prevent or treat any given type of cancer.

To begin, the prevention of cancer, a disease affecting so many different types of cells, tissues, and/or organs, is an intractable proposition, if not now wholly impractical, given, for example, that it is such a heterogeneous disease, having widely varying pathologies and etiologies, and that its causes are multifactorial and as yet only partially characterized and poorly understood. It is generally recognized that a disease cannot be prevented unless and until its causes are fully appreciated and understood to a degree that it becomes possible to intercede effectively to block its onset or development. As such, the information contained in the specification, which too inadequately describes the claimed inventions that are useful for preventing any of the large plurality of such disparate types of cancer, would not be sufficient to permit their immediate use by the skilled artisan in the intended manner to prevent any specific type of cancer in the mammal treated using the inventions.

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prevention or treatment of a disease caused by a pathogenic organism, wherein the antigen is an antigen

To further explain, as of yet, the art of preventing cancer, or more particularly any specific type thereof, has met with little if any success.

Very recently Lollini et al. (*Curr. Cancer Drug Targets.* 2005 May; **5** (3): 221-228) disclosed a complete prevention of mammary carcinoma was obtained in transgenic mice predisposed to this cancer by immunization with the so-called "triplex vaccine"; see entire document (e.g., the abstract). Even so, Lollini et al. teaches, "[m]ost current tumor antigens appear to be unsuitable targets for cancer immunoprevention" (abstract), since most are not have "crucial pathogenetic role in tumor growth" and/or are ineffective to stimulate both arms of the immune system (e.g., abstract). Lollini et al. (*Trends Immunol.* 2003 Feb; **24** (2): 62-66) explains although medicine in the postgenomic era offers an increasing possibility of detecting healthy individuals at risk of developing cancer who could benefit from tumor preventive vaccination, the identification of tumor antigens suitable for inclusion in such vaccines should require the tumor antigen have a crucial pathogenetic role for tumor growth to avoid the selection of antigen-loss variants (abstract).

Notably, the specification discloses that the antigen used might be alpha-fetoprotein (AFP) or an immunogenic portion thereof, which has been described as an antigen associated with hepatocellular carcinoma[5]; yet, only a proportion of hepatocellular carcinomas (HCC) express AFP. This would suggest that AFP is not a suitable antigen for use in chemoprevention of HCC.

In addition, as explained by Abelev et al. (*Semin. Cancer Biol.* 1999 Apr; **9** (2): 95-107), the gene encoding AFP is expressed normally during early development and again during liver regeneration, but AFP expression in HCC is transitional and variable; see entire document (e.g., the abstract and page 102, columns 1 and 2). Abelev et al. teaches an example of HCC cells that transitioned from AFP-positive status to AFP-negative status, but without loss of their biological properties, and another example in which it proved possible to isolate both AFP-positive and AFP-negative clonal variants from the same tumor line (page 102, column 2). Abelev et al. teaches the frequency of

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associated with a tumor.

such transitioning from AFP^+ to AFP^-, and vice versa, is very high, and much higher than that which would be expected from conventional mutations (page 103, column 1). This process by which transitioning occurs is not understood, but Abelev et al. suggests it is the end result of a chain of developmental events occurring during epigenesis, leading from cellular genotype to phenotype after the initial action of one or a plurality of associated genes (page 103, column 1). Abelev et al. teaches the reason for the tremendous variations in the levels of AFP produced by hepatomas is better understood (page 103, column 1, through page 104, column 1). Regardless of the mechanisms by which such transition and variation occur in HCC, the description thereof by Abelev et al. suggests AFP does not have the requisite crucial role in its pathogenesis to be considered a candidate for use in chemopreventive therapy of HCC.

This example illustrates the fact that despite the structural complexity of the fusion protein that is encoded by the claimed nucleic acid molecules, it is the at least one antigenic peptide comprising an MHC class I epitope that necessarily achieves the effect of stimulating immunity against the antigen, so as to prevent or treat the disease in the mammal. Thus, the issue of utility largely involves the determination of the identity of the antigen that is used to effectively immunize the mammal in order to prevent or treat the disease; the other components of the fusion protein are not as important inasmuch as, for the most part, specificity is determined by the antigenic component, and not these other components. Accordingly, antigen's identity is critical to any evaluation of the purported utility of the claimed inventions to treat any particular type of cancer (or infectious disease).

Consider the case with melanoma, for example, a type of cancer that affects melanocytes. Bins et al. (*J. Immunother.* 2007 Feb-Mar; **30** (2): 234-239) fairly recently described the results of a phase I clinical trial of a vaccine comprised of not one, but three peptides derived from melanoma-associated antigens, only to conclude that none of the patients responded clinically; see entire document (e.g., the abstract). Bins et al. comments that the efficacy that was observed "was disappointingly low" (abstract); and

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[5] See, e.g., paragraph [0051] of the published application.

states, "[in] accordance with previously published vaccination studies, these results add to the increasing evidence that peptide vaccination in itself is not potent enough as an effective melanoma immunotherapy in advanced-state patients" (abstract).

Thus, despite whatever progress may have been made in the past few years, treatment of melanoma, for example, by immunotherapy remains largely unsuccessful[6]; it follows that it would be wholly unreasonable to presume that such methods might prevent the occurrence of the disease altogether in mammals and that the clinical utility of such methods to effectively treat the disease has yet to be established.

Perhaps in time the pitfalls that hamper successful application of such treatments might be avoided, but at present it is apparent that the specification, as filed, would not permit the skilled artisan to immediately use the claimed products and processes in the manner intended by Applicant.

The identity of the antigen is not the only factor that will determine the effectiveness of the claimed inventions when used as intended to prevent (or treat) cancer or any non-cancerous infectious disease by stimulating an immune response against tumor cells or the causative pathogens (e.g., bacteria). The genotype of the mammal (e.g., the human patient) is also important, as explained in the following paragraphs.

Certainly not all patients are to be considered for prophylactic therapy using the claimed inventions, because only some patients will even have a potential to benefit from such therapy. Supporting this position, Yamshchikov, et al. (*Clinical Cancer Research* 2001; **7**: 909s-916s) teaches that three of four HLA-A3 typed patients, each diagnosed with rapidly progressing melanoma, had no detectable CTL response following vaccination with an immunogenic peptide. Not surprisingly, the one patient that did have peptide-responsive CTL was the long-term surviving melanoma patient, i.e., Patient VMM18 from whom the peptide was originally isolated. Because the peptide was isolated from the tumor-infiltrating lymphocytes (TIL) recovered from a

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[6] Mellman (*The Scientist* 2006; **20** (1): 47) teaches that therapeutic vaccines for cancer have been disappointing with the response rate of roughly 1,000 patients is below 4%; see entire document (e.g., page 47, second paragraph).

tumor-involved nodal biopsy, lymphocytes isolated from the nodal biopsy would, of course, be expected to respond to peptide stimulation *in vitro*. Less understandably, despite the other patients being HLA-A3+, none of the lymphocytes isolated from their nodal biopsies responded *in vitro*. Obviously, the presence of a particular HLA type of class I MHC molecules is not the only criterion that determines whether an individual should be treated using the invention.

To explain, cytotoxic T cells (CTL) bind to antigen-presenting cells (APC) and under specific circumstances will become activated. Simplistically, the CTL and the APC interface by the highly specific formation of a trimolecular complex comprising the antigenic peptide "primed"-class I MHC molecule, displayed at the surface of the APC, and the T cell receptor (TCR), displayed at the surface of the CTL. Every individual has a relatively unique "repertoire" of T cells or clones, where each clone has a different TCR, which has a different antigenic binding specificity. Thus, some individuals' repertoires may be deficient in one or more CTL that, if present would be activated by the claimed immunogen. Those patients lacking the appropriate CTL clone will not benefit from the prophylactic or therapeutic use of the invention.

It appears that the specification fails to provide a means to identify the population of individuals with whom the invention can be used as intended to prevent or treat any given type of cancer or infectious disease.

Accordingly, because the specification fails to disclose a means for identifying or selecting appropriate candidates for treatment using the claimed inventions, and regardless of the identity of the antigen, it is submitted that the claimed inventions could not immediately be used by the skilled artisan in the manner intended so as to benefit the public; and as that is the case, as explained above, the claims fail to satisfy the utility requirement set forth under 35 U.S.C. § 101.

Turning now to the issue of the therapeutic vaccine, which is intended for use in treating (not preventing) cancer or infectious disease, while there are vaccines that prevent some infectious diseases, few treat those diseases, and while many cancer

vaccines have been placed in clinical trials, the results thus far have been disappointing and even discouraging.

It has become evident that simply stimulating an immune response against a given antigen that is associated with a particular type of cancer, for example, is more often than not ineffective to treat the disease. There are a variety of different reasons that this is likely the case, some of which are discussed in the paragraphs that follow, but in view of such limitations and failure it is submitted that the claimed inventions could not immediately be used to treat any one particular disease, so as to satisfy the utility requirement.

Supporting this position, Wang et al. (*Exp. Opin. Biol. Ther.* 2001; **1** (2): 277-290) teaches the "melanoma model" is the paradigm for studies of the effectiveness of T-cell-directed cancer vaccines; see entire document (e.g., the abstract). Wang et al. teaches, "the success of these approaches has been limited [save for scattered reports] and T-cell-directed vaccination against cancer remains at a paradoxical standstill whereby anticancer immunisation can be induced but it is not sufficient, in most cases, to induce tumour regression" (abstract). In order to explain the lack of clinical success, despite the promise of preclinical data, Wang et al. teaches, among other reasons, clinical data suggest the possibility of a dissociation between immune responses detected in peripheral blood *versus* tumor, which suggests that is more important to determine immune response at the tumor site, rather than in the peripheral blood, in assessing the likely effectiveness of the treatment (page 281, column 1). Regardless of the cause for such poor extrapolation of preclinical findings, Wang et al. discloses the difficulty of correlating laboratory findings with clinical outcome is a significant obstacle to the assessment of the role of immune escape and/or tolerance in cancer progression (page 282, column 2). Furthermore, Wang et al. teaches, "[t]he published experience using the ELISPOT [assay] to monitor T-cell responses to cancer antigens is still limited" (page 283, column 2); and Wang et al. teaches the same is true of the "tetramer" assay (page 284, column 2). Wang et al. teaches, "there are no universally accepted correlates at this time between any method of in vitro immune monitoring and clinical outcome" (page 285, column 1).

Thus, due in part to the inadequacy of the methods used to assess the immune response mustered upon vaccination and the poor correlation of such results and clinically relevant endpoints, such as tumor regression, the art of cancer immunotherapy is highly unpredictable. Bodey et al. (*Anticancer Research.* 2000; **20**: 2665-2676) teaches, "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy" (page 2665, column 2). As to the current state of the art, Bodey et al. comments, "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (page 2668, column 2). Thus, little has changed to alter the artisans' expectations of the still prospective immunotherapy since the invention was made. Cox et al. (*Science.* 1994; **264**: 716-719) teaches, "neither adoptive transfer of melanoma-specific CTLs nor specific active immunotherapy with whole melanoma cells or cell-derived preparations has led to the eradication of melanoma in more than a minority of patients" (page 716, column 2). Then again, even that small note of promise has since faded. Bodey et al. discloses, "ASI in at least one instance may have cured melanoma in a patient with metastatic disease, but that patient developed another immunologically and genetically distinct melanoma" (page 2668, column 2). In the abstract Bodey et al. speculates upon the reasons that ASI is ineffective or lacks efficacy:

> The theoretical basis for all of these approaches is very well founded. Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained with a cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs [tumor associated antigens] in the context of the particular human leukocyte antigen (HLA) subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use.

The goal of anti-tumor vaccination is the induction of anti-tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (*Journal of NIH Research.* 1995; **7**: 46-49) states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph). Ezzell further teaches that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micro-metastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (page 48, paragraph 6). Published more recently, Bodey et al. (*supra*) states, "there should be caution about assuming that a single epitope or even a few epitopes combined will be as effective 'crude' materials, which might better be thought of as 'polyvalent'" (page 2668, column 2). Spitler (*Cancer Biotherapy.* 1995; **10**: 1-3) recognizes the lack of predictability of the nature of the art when she states, "ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: 'cancer vaccines don't work'. Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response" (page 1, paragraph 1).

Whatever avenue the artisan takes, in view of the unpredictability in the art, the rarity and lack of uniformity in the successful application, and the numerous and substantial limitations encountered, the threshold of enablement is high. To fulfill the utility requirement, the specification must enable one of skill in the art to make and to use the invention as it is intended with a reasonable expectation of success and without the need to first further elaborate upon the disclosure to complete the inventive process to discover how (or if) the invention can be so used.

In many instances, to have success, the use of the invention must elicit a tumor-specific CTL response against the antigen. Boon (*Advances in Cancer Research*. 1992; **58**: 177-210) teaches that for successful application of active immunization in human patients, we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have already occurred in the patient and in such cases, active specific immunization will be fruitless,

since anergic TCL cannot be activated, will not proliferate, and are deficient in effector function. Several lines of evidence suggest that large tumor burdens can tolerize, or at least depress the capability to respond against the tumor (page 206, paragraph 2). Furthermore, among other mechanisms, Arceci (*Journal of Molecular Medicine.* 1998; **76**: 80-93) teaches, "it has been hypothesized that tumor cells may escape immune recognition and subsequent killing by failing to satisfy one or more of the [...] requirements for T cell antigen recognition and activation. For example, if antigen presentation does not occur because of low or absent expression of MHC or lack of a recognizable tumor antigen, then tumor cells would not be recognized" (page 83, column 2). Areci continues, "on the other hand, if antigen recognition occurs by T cells but tumor cells do not express a costimulatory molecule, then T cells might become anergic to the tumor cells" (page 83, column 2). Notably, Areci teaches, "most solid tumors usually do not express costimulatory molecules" (page 84, column 1); therefore, it is unlikely that the invention can be used to effectively immunize a patient against most cancers.

There is considerable art indicating that cancer vaccines are ineffective, *even if antigen-specific T-lymphocytes can be activated by immunization protocols*. Lee et al. (*Journal of Immunology.* 1999; **163**: 6292-6300) teaches, "although comparative ex vivo sensitization of pre- and postvaccination PBMC [peripheral blood mononuclear cells, such as B- and T-lymphocytes] has identified reproducible, vaccine-specific systemic T cell responses to immunization, in the majority of cases no regression is seen" (page 6292, column 1). In studies similar to those that are set forth in the examples in the specification, Lee et al. teaches that melanoma antigen epitopes were identified and that these peptide epitopes were capable of inducing highly specific T cell responses against autologous and some HLA-matched tumor cells. Lee et al. discloses that "these studies gave the impression that vaccines induce powerful immunizations comparable to those demonstrable against common pathogens such as the influenza virus to which individuals are repeatedly exposed throughout their lifetime". However, "in most cases, this **vaccine-induced T cell reactivity still does not lead to tumor regression**" (emphasis added) (page 6299, column 1). One of the reasons for the discrepancy, Lee

et al. suggests, may be that in vitro methods, which are commonly used to assess immune post-vaccination immune response, such as cell-mediated cytotoxicity assays, tend to "overestimate quantitatively the strength of the immune reaction within the organism" (page 6299, column 1). Lee et al. catalogs a variety of possible explanations for the lack of efficacy, including clonal deletion, exhaustion, or senescence, which are implicated in the development of systemic, epitope-specific immune tolerance, and inadequate immune response attributable to decreased T cell receptor signaling capacity or circulating immune-suppressive cytokines, but conclude that their data suggest that the extent rather than the quality of the response might be more significant limitation of the vaccination protocol (page 6299, column 2). More specifically, Lee et al. reports, "we were surprised at the relatively low numbers of CTL precursors after vaccination even in patients' samples that boasted an exceptional epitope-specific expansion in vitro" (page 6299, column 2). Lee et al. summarizes their study, teaching that "a peptide-based vaccine can effectively generate a quantifiable T cell-specific immune response in the PBMC of cancer patients, though such a response does not associate with a clinically evident regression of metastatic melanoma" (abstract). While Lee et al. refers specifically to the treatment of melanoma using a different epitope, the teachings are highly germane to the enablement issues relevant in the instant application, because the severe limitations will undoubtedly be shared by any protocol that uses the claimed invention, and there is no exemplification in the specification that would suggest otherwise. In yet another example, Zaks et al. (*Cancer Research.* 1998; **58**: 4902-4908) teaches that immunization of patients diagnosed with cancer with a peptide epitope derived from the tumor antigen HER-2/neu/ErbB2 leads to activation of peptide-specific cytotoxic T-lymphocytes, but that the T-lymphocytes fail to recognize tumor cells that express the antigen. Zaks et al. discloses their experience is not unique (page 4907, column 2). Gao et al. (*Journal of Immunotherapy.* 2000; **23**: 643-653) discloses the finding that, although antitumor CTL response was enhanced by immunization, the tumors failed to regress. Gao et al. teaches that the observed lack of regression was associated with a lack of CTL migration to the tumor sites (abstract).

Thus, activation of peptide epitope-specific CTL *is not an appropriate endpoint* and a prediction or estimation of efficacy based only upon such data is imprudent or inexact.

Moreover, many attempts to provide efficacious therapeutic or prophylactic immunotherapy for cancer patients have paradoxically failed; despite evidence of that vaccination has induced proliferation of tumor antigen-specific CTL, no major protective antitumor response was seen over and over again in these cases. See, for example, Hu et al. (*Cancer Research.* 1996; **56**: 2479-2483); Jaeger et al. (*International Journal of Cancer.* 1996; **66**: 162-169); Mukherji et al. (*Proceedings of the National Academy of Science USA. 1995;* **92**: 8078-8082); and for review, see Bocchia et al. (*Haematologica*. 2000; **85**; 1172-1206).

Moreover, many attempts to provide efficacious therapeutic or prophylactic immunotherapy for cancer patients have paradoxically failed despite evidence of that vaccination has induced proliferation of tumor antigen-specific CTL, as no major protective antitumor response was seen in these cases. There are many reasons that the promise of pre-clinical endeavors is broken once clinical trials ensue. Among the possible reasons, with regard to animal models, tumors tend to be highly immunogenic and thus quite unlike most human cancers. Gura (*Science.* 1997; **278**: 1041-1042) discusses the limitations of animal and cell models. Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs). Sadly, Gura reports that using xenograft animal models to evaluate the potential of novel antitumor therapies often leads to the discovery of " 'good mouse drugs rather than good human drugs' " (page 1041, column 2), because the results acquired using animal models or cell culture are not correlative with those acquired in the clinic. Additionally, with regard to lack of correlation, Lee et al. (*supra*) cautions, "it is likely that the immune responses judged after ex vivo expansion of postvaccination PBMC overestimate quantitatively the strength of the immune reaction within the organism" (page 6299, column 1); and Wang et al. (*supra*) similarly comments upon the inadequacy of assessing immune response by the methods at hand. The magnitude of the immune response that might be

sufficient to protect a mammal against a tumor is unknown. Finally, Bodey et al. (*supra*) teaches despite promising, even tantalizing results *in vitro* and *in vivo*, especially with animal models, the failure of cancer vaccines is predicated by very relationship between the tumor and the host immune system, which effectively makes the use of cancer vaccines futile:

> Malignant tumors undergo constant microevolution. Natural selection of the most advantageous surface IP [immunophenotype] involves constant modulation of previous IPs. Progressive dedifferentiation characterizes all neoplastically transformed cells. During this process, numerous 'novel' cell surface antigens appear, are modified and thus do not present the host's immune system with some immunogenic elements. The leukocytic inflammatory infiltrate contains cells with divers capabilities including neutrophils, macrophages and other professional APCs [antigen-presenting cells], as well as T lymphocytes. In situ activation of TAA [tumor-associated antigen] specific CTL [cytotoxic T-lymphocyte] clones occurs and thousands of tumor cells are lysed. However, as we would expect from any population in danger of extinction, the cells of the neoplastically transformed mass proceed with their microevolution and numerous clones of tumor cells survive each repeated attack by the immune system through secretion of immunoinhibitory cytokines, downregulation of MHC molecules, loss of costimulatory molecules, and induction of clonal T cell anergy, among other as yet uncovered ways. This process continues until the 'creation' (ironically as it may sound, by the host's immune system) of highly resistant, poorly immunogenic, and extremely aggressive clones of tumor cells. This is the reality of cancer progression: a back-and-forth struggle between host and tumor, with evolutionary dynamic exchanges throughout the entire process. Use of cancer vaccines to stimulate the immune system may be in vain" (citations omitted) (pages 2673-2674).

Consistently, Slinghuff et al. (*Cancer Immunol. Immunother.* 2000 Mar; **48** (12): 661-672) reports concordant loss of expression of multiple "melanoma antigens" (i.e., tyrosinase, gp-100, Trp-1, and MART-1) by melanomas; see entire document (e.g., abstract). Such loss of expression of these proteins by melanomas evidences their dispensability or lack of importance, suggesting they are unsuitable targets for cancer immunoprevention or therapy.

Addressing a different issue now, it is noted that many of the claims are directed to vaccines comprised of nucleic acid molecules, as opposed to engineered antigen presenting cells (APCs) expressing the claimed nucleic acid molecules encoding the fusion polypeptides. Whereas the claimed engineered APCs might be used in adoptive immunotherapeutic regimens involving the transfer of the cells to the subject or patient, it is apparent that the claimed vaccine is intended for use in preventing or treating

cancer or infectious disease as a formulation of naked DNA or vector; accordingly, the claims read on products intended for use in treatment processes termed by the art as "gene therapy".

The art of gene therapy, i.e., the *in vivo* delivery genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, is still in its infancy. Moreover, the art is highly unpredictable and its successful application has been hindered by numerous limitations, which the specification does not remedy and would preclude the skilled artisan from having a reasonable expectation of making and immediately using the claimed invention as is intended without first elaborating upon the disclosure to complete the inventive process and discover how the invention can specifically be used to prevent or treat cancer or an infectious disease.

For example, the teachings of the specification have not overcome the problems with *in vivo* delivery and expression. Verma et al. (*Nature* 1997, **389**: 239-242) teaches that the Achilles heel of gene therapy is gene delivery (page 239, column 3). Verma et al. states that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression; see entire document (e.g., page 239, column 3). Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, **2**: 111-133) teaches that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies; see entire document (e.g., page 111, column 2). In addition, Amalfitano et al. discusses numerous limitations that have been encountered in using retroviral vectors to deliver DNA into a subject and teaches the use of adenoviral vectors can be ineffective because of the induction of strong immune responses in the host to the viral vectors and direct acute and chronic toxicity caused by the vector itself; see entire document (e.g., abstract).

It is noted that Amalfitano et al. teaches that a despite general lack of success, the first conclusive evidence that gene therapy can show efficacy in humans was achieved in human X-linked SCID subjects *via* retrovirus transduction (page 111, column 2). However, since the publication, The Department of Health and Human Services has released a memorandum dated January 14, 2003, a copy of which is attached to this Office action, that urges all such investigations to be discontinued until

new data are available, the possible etiology and risks of adverse events associated are considered, and recommendations emerge. Despite the initial promise of the trial studying gene transfer as a possible treatment for the disease, investigators have found that retroviral-mediated insertion of the transgene has caused the subjects to develop cancer. The results of the trial underscore the high degree of unpredictability associated with the art and the fact that the skilled artisan could not make or use the claimed invention with a reasonable expectation of success without need to perform additional and an undue amount of experimentation.

The state of the art, as a whole, is well defined by Pandha et al. (*Current Opinion in Investigational Drugs* 2000; **1** (1): 122-134). Pandha et al. teaches:

> Despite the rapid technological advances that continue to sustain the field of cancer gene therapy, few individual patients have benefited from the revolution so far. The plethora of clinical trials described confirms that each malignancy will have its own ideal strategy based on the associated molecular defects, and there has been rapid progress from this viewpoint. At the same time, there has been a renewed appreciation for the limitations to gene therapy, which include low efficiency of gene transfer, poor specificity of response and methods to accurately evaluate responses, and lack of truly tumor-specific targets at which to aim. As with all new therapies, we are climbing a steep learning curve in terms of encountering treatment-related toxicities, as well as profound ethical and regulatory issues (abstract).

Then, although the claims are not so limited, it is noted that the disclosure teaches the inventions comprise, for example, an antigen associated with lung cancer, which might be used to prevent or treat lung cancer; yet, it is also noted that Ferrari et al. (*Clin. Exp. Immunol.* 2003; **132**: 1-8), for example, addresses the immunological hurdles to lung gene therapy, which continue to hinder the successful clinical application of such treatments and yet which have not been resolved by the instant disclosure; see entire document (e.g., the abstract). Ferrari et al. teaches that although gene transfer to the lung is feasible, gene expression from both viral and non-viral vectors has been inefficient and inflammatory, antibody, and T cell responses limit transgene expression duration and readministration (abstract), just as earlier published references also indicate.

So, despite advancements in the art of gene therapy, the same limitations that hindered its successful therapeutic application in past years continue to hamper its clinical use today.

Furthermore, it is submitted that with each different organ system, and with each different embodiment of the claimed invention, it is apparent that there are different issues pertaining to delivery and uptake of vaccines comprising naked DNA or viral vectors, which in any case could not be used as intended to prevent or treat any of the different types of cancer or infectious diseases affecting the organ system without first completing the inventive process to discover how, if at all, the desired prophylactic or therapeutic effect can be achieved.

In conclusion, as explained, in order to satisfy the utility requirement set forth under 35 U.S.C. § 101, the claimed inventions must have a "specific and substantial" asserted utility, which is specific to the particular nature and substance of the claimed subject matter, and which would be immediately available for application in a "real-world" context by virtue of the existing information disclosed in the specification and/or on the basis of knowledge imparted by the prior art, such that its use would not require or constitute carrying out further research to identify or reasonably confirm its usefulness in this context. However, as is this case here in view of the preponderance of factual evidence now of record that cancer vaccines are largely ineffective to prevent or treat the disease, it seems that the utility requirement has not be met. If any embodiments of the claimed inventions, which are readily used as is intended to prevent or treat cancer or an infectious disease upon issue of a patent from this application are disclosed in this application it is not apparent which ones those are and thus the claimed inventions could not immediately be used as intended to yield prophylactic or therapeutic benefit without the need to first elaborate upon the disclosure thereof to discover which, if any, of the inventions can be so used to prevent or treat which particular diseases.

Claim Rejections - 35 USC § 112

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 1, 3, 5, 11-44, 47-53, 56, and 57 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

As explained in the above rejection of the claims under 35 U.S.C. § 101, the claimed invention is not supported by a specific and substantial asserted utility, or a well-established utility, as the asserted utilities are either not specific to the substance and nature of the claimed antibody or could not be practiced in a manner that might immediately benefit the public.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue”. These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to

practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

In this case, it is submitted that the skilled artisan would not know how to use the claimed invention in any specific manner, as intended, to prevent or treat any one particular type of cancer or an infectious disease; and if there is an embodiment of the claimed invention that could be used in the manner intended it is not immediately which embodiment that is, as there are so very many too inadequately described to recognize without the need to first complete the inventive process to discover which ones those are. Moreover, it is apparent that the amount of guidance, direction, and exemplification disclosed in the specification is not reasonably commensurate in scope with the claims; and in fact, it is duly noted that there are no disclosures in this application pertaining to any exemplifying experiments or studies to show that the claimed inventions can be used as intended to prevent or treat cancer or infectious disease. The specification would at best only reasonably permit the claimed products to be made, but not used without undue experimentation. Nonetheless, because the art is so highly unpredictable, in the absence of an amount of guidance, direction, and exemplification that is reasonably commensurate in scope with the claims, the skilled artisan would not accept the assertion that the claimed invention can be used to prevent or treat any given type of cancer or infectious disease. Consequently, if a patent were to issue upon this application, given only the disclosure therein, one skilled in the art would not know then how to use the claimed invention in a manner that might immediately benefit the public. As such, a patent granted upon this application could only be viewed as a mere invitation to the skilled artisan to elaborate a use for the claimed invention, or to finish the inventive process. The need to elaborate such a use for the claimed subject matter or to finish the inventive process would constitute a requirement that the practitioner perform an undue amount of experimentation before the claimed invention could be made and used in a manner that might ultimately benefit the public, or with a reasonable expectation of success.

20. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

21. Claims 1, 3, 5, 11-31, 38, 39, 49-51, and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In accordance with a recent decision by the Federal Circuit (*Halliburton Energy Services Inc. v. M-I LLC*, 85 USPQ2d 1654, 1658 (Fed. Cir. 2008)):

> 35 U.S.C. § 112, ¶ 2 requires that the specification of a patent "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." Because claims delineate the patentee's right to exclude, the patent statute requires that the scope of the claims be sufficiently definite to inform the public of the bounds of the protected invention, i.e., what subject matter is covered by the exclusive rights of the patent. Otherwise, competitors cannot avoid infringement, defeating the public notice function of patent claims. Athletic Alternatives, Inc. v. Prince Mfg., Inc., 73 F.3d 1573, 1581 (Fed. Cir. 1996) ("[T]he primary purpose of the requirement is 'to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their [respective] rights.'") (quoting Gen. Elec. Co. v. Wabash Appliance Corp., 304 U.S. 364, 369, (1938)). The Supreme Court has stated that "[t]he statutory requirement of particularity and distinctness in claims is met only when [the claims] clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." United Carbon Co. v. Binney & Smith Co., 317 U.S. 228, 236 (1942).

Claims 1, 3, 5, 11-31, 38, 39, 49-51, and 53 are indefinite for the following reasons, thereby failing to satisfy the requirements set forth under 35 U.S.C. § 112, second paragraph:

(a) Claim 1, for example, is directed to a polypeptide that is capable of "high level presentation of antigenic peptides on antigen-presenting cells"; yet, it cannot be ascertained relative to what standard of comparison a determination of the level of presentation of antigenic peptides by the APCs must be made, so as to know whether or not the level is considered "high".

This is apparently important since it is presumed that not all polypeptides are capable of "high level presentation of antigenic peptides on antigen-presenting cells"; and since the claims are directed to only those that are, it is imperative that the artisan be reasonably apprised as to the identities of those that are or otherwise have means for determining which polypeptides are encompassed by the claims, and which are not.

Even so, it also cannot be ascertained under what relative conditions the polypeptide must be *capable of* such high level presentation, if not always. When and why are the claimed polypeptides said to have such capability, especially when it would seem that the presentation of antigenic peptides is a function of the cell and not the polypeptide?

For these reasons, it is submitted that the claims are too vague and fail to delineate claimed subject matter with the requisite clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, so as to satisfy the requirements set forth under 35 U.S.C. § 112, second paragraph.

(b) Claims 14 and 23 recite the limitation “said antigen”, which in both cases does not find antecedent basis in the language of the preceding claims. Therefore, it cannot be ascertained to which antigens the claims are directed.

(c) Claim 53 is indefinite because the claim recites the limitation "the antigen", but the preceding claim is directed to more than one antigen and it is not clear to which antigen claim 53 refers.

(d) Claims 1, 3, 5, 11-31, 38, 39, 49-51, and 53 are indefinite because the claims use of the designations such as “CD40’, “MAGE” and “gp100” as the sole means of identifying the polypeptides or antigens to which the claims refer. The use of laboratory designations only to identify a particular polypeptide or a family of polypeptides renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct polypeptides.

For example, the terms “MAGE” and “BAGE” do not identify a single particular polypeptide but rather a family of structurally and functionally disparate family members.

Although some members of a given family may be associated with cancer (e.g., are overexpressed by cancer cells relative to normal cells of the corresponding tissue or organ), other members are not.

De Plaen et al. (*Immunogenetics.* 1994; **40**: 360-369), for example, reviews the structure, chromosomal localization and expression of twelve genes encoding members of the MAGE family of proteins; see entire document (e.g., the abstract). De Plaen et al. teaches six of the members of the gene family were found to be expressed at a high

level in a number of tumors of various histological types; while five were very weakly expressed in all samples tested, and one, namely MAGE 7, was not transcribed at all in the ninety-five tumor samples tested (page 367, column 1).

Just as not all members of the MAGE family of proteins are associated with cancer, particularly, since is it not obvious what, if any, association the weakly expressed MAGE proteins have, it is apparent that the use of the term "MAGE" alone to identify the antigens that are regarded as part of the invention should not be considered sufficient to delineate the subject matter with the requisite clarity and particularity to satisfy the requirements set forth under 35 U.S.C. § 112, second paragraph. The same is true of any other such terms, which identify not particular polypeptides but rather any of a plurality of structurally and/or functionally disparate polypeptides, even if they are related as members of a given family.

Thus, it is apparent that the same term is often used in the art to describe not one polypeptide, but rather a plurality of polypeptides, which might be structurally and/or functionally related, but otherwise distinct. As another example, it is noted that the same terms are often used to describe various isoforms that are encoded by a single gene, which result from translation of alternatively spliced transcripts of that gene; as another example, the same terms are frequently used to identify polypeptides that occur in different species of animals, which although sharing certain structural and/or functional characteristics have distinct structures and/or functions (e.g., orthologs and paralogs).

The term "CD40", for example, identifies not just one particular polypeptide, but rather any of a number of orthologs encoded by genes in different mammals.

The same is true of the term "human CD3 ζ polypeptide", which has been described as having a number of structurally and functionally disparate isoforms. Tsuzaka et al. (*Springer Semin Immunopathol.* 2006 Oct; **28** (2): 185-193), for example, describes mRNA slice variants encoding variant forms of the polypeptide that have been observed in the peripheral blood T cells from systemic lupus erythematosus patients; see entire document (e.g., the abstract). Not dissimilarly Atkinson et al. (*Biochem Biophys Res Commun.* 2003 Oct 24; **310** (3): 761-766) also describes

isoforms of human CD3 ζ polypeptide encoded by an alternatively spliced mRNA in T cells or natural killer cells, which have altered signal transducing activities as compared to other isoforms; see entire document (e.g., the abstract).

35 U.S.C. § 112, second paragraph, requires the claim define the metes and bounds of the subject matter that is regarded as the invention with such clarity and particularity to permit the skilled artisan to know or determine infringing subject matter; because the terms used to describe the polypeptides to which the claims are directed do not unambiguously identify those polypeptides, this requirement has not been met.

It is suggested that this issue might be remedied by amending the claims to include a recitation of the amino acid sequence of the polypeptides by reference to one or more specific sequence identification numbers of amino acid sequences set forth in the Sequence Listing because the amino acid sequence of a polypeptide is a unique identifier that unambiguously defines a given polypeptide.

(e) Claim 19 is indefinite because the claim recites the HLA-2 binding peptide derived from gp100 and the gp100 HLA-A3 binding peptide are selected from the group consisting of the amino acid sequences identified by the claims, but it cannot be ascertained if the claimed peptides comprise *or* consist of any of these amino acid sequences. For this reason, the claim fails to delineate the metes and bounds of the subject matter that is regarded as the invention with the requisite clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, so as to satisfy the requirements set forth under 35 U.S.C. § 112, second paragraph.

22. Claims 1, 3, 5, 11-44, 47-53, 56, and 57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines

for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In this instance, the claims are directed to a nucleic acid molecule encoding a fusion polypeptide comprising a β2-microglobulin molecule adjoined to a peptide that spans the distance from the C-terminus of the β2-microglobulin molecule to the cell membrane, which in turn is adjoined to a "sequence" that anchors the entire fusion polypeptide to the cell membrane and which consists of the full or partial transmembrane and/or cytoplasmic domain of a molecule selected from the group consisting of the human CD3 ζ polypeptide, CD40 and the MHC class I heavy chain of HLA-A, HLA-B, or HLA-C.

Contrary to any such assertion, the cytoplasmic domain of any of the human CD3 ζ polypeptide, CD40 and the MHC class I heavy chain of HLA-A, HLA-B, or HLA-C, which is adjoined to a peptide that spans the distance from the C-terminus of the β2-microglobulin molecule to the cell membrane, will not span the membrane or exert the requisite anchoring function. The presence of a transmembrane domain is essential.

Then, also contrary to the assertion, a peptide consisting of a mere portion (e.g., an amino acid) of a transmembrane domain of a protein, such as the human CD3 ζ polypeptide is not capable of exerting the required anchoring function. Moreover, it is submitted that the entireties of most transmembrane domains of protein, such as the human CD3 ζ polypeptide would necessarily be adjoined to the peptide that spans the distance from the C-terminus of the β2-microglobulin molecule to the cell membrane, so as to allow the anchorage of the fusion polypeptide to the cell membrane; and in fact such fusion polypeptides comprising the entireties of the transmembrane domains appear to be the only members of the claimed genus that are described in this application with the requisite clarity and particularity to reasonably convey their possession by Applicant as of the time the application was filed. No portions of the transmembrane domains of any of the human CD3 ζ polypeptide, CD40 and the MHC class I heavy chain of HLA-A, HLA-B, or HLA-C, which are sufficient to permit anchoring

of the fusion polypeptide comprised of those portions to the cell membrane of cells expressing the claimed polynucleotide encoding the fusion polypeptide, are described in this application. Furthermore, the entireties of the transmembrane domains of the polypeptides described should not be deemed representative of the far more broadly claimed portions thereof that are only described as necessarily exerting the required function. The extent of any portions of the transmembrane domains of the human CD3 ζ polypeptide, CD40 and the MHC class I heavy chain of HLA-A, HLA-B, or HLA-C, which can be adjoined to the peptide that spans the distance from the C-terminus of the β2-microglobulin molecule to the cell membrane, so as to allow the anchorage of the claimed fusion polypeptide to the cell membrane, cannot be predicted but must be determined empirically.

Accordingly, Applicant is reminded that the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

In addition, Applicant is duly reminded that "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

In this instance, there is no language that adequately describes with the requisite clarity and particularity the fragments of the transmembrane domains of any of the human CD3 ζ polypeptide, CD40 and the MHC class I heavy chain of HLA-A, HLA-B, or HLA-C, which are sufficient to permit anchoring of the fusion polypeptide comprised of those fragments that are only described as necessarily being capable exerting the required anchoring function. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

This is in part because the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability exert

the requisite anchoring function, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). The claimed method depends upon finding the portions of the transmembrane domains of any of the human CD3 ζ polypeptide, CD40 and the MHC class I heavy chain of HLA-A, HLA-B, or HLA-C, which are sufficient to permit anchoring of the fusion polypeptide comprised of those fragments; without such those portions, which are essential parts of the claimed invention, it is impossible to practice the invention.

In addition, although the skilled artisan could potentially identify portions of the transmembrane domains of any of the human CD3 ζ polypeptide, CD40 and the MHC class I heavy chain of HLA-A, HLA-B, or HLA-C, which are sufficient to permit anchoring of the fusion polypeptide comprised of those fragments, by screening a plurality of structurally different portions of the domains to identify those that are capable of exerting the requisite anchoring function, it is duly noted that the written description

provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Turning now to a different issue, since the claimed polynucleotide encodes a fusion polypeptide comprising a β2-microglobulin molecule adjoined via its amino-terminus to an antigenic peptide comprising an MHC class I epitope, wherein the peptide is *derived* from any of a large number of structurally and functionally disparate antigens, which are associated with cancer or an infectious disease caused by a pathogenic organism, including any given bacterium, virus, fungus or parasite, it is aptly noted that the claims are directed to a genus that cannot be said to be adequately represented by those peptides that are particularly described by the specification. This is in part because the peptide need only be derived from any of the aforementioned antigens, the structure of the peptide of which the fusion polypeptide encoded by the claimed polynucleotide need not have any particular structure. Given this fact, no one particularly identified peptide (e.g., the peptide of SEQ ID NO: 4, which according to claim 16, e.g., is an antigen derived from AFP, a tumor associated antigen) should be regarded as representative of the genus of antigenic peptides, as a whole, and especially not of the genus that can be so variously used in constructing fusion polypeptides that will be suitably used to achieve the claimed prophylactic or therapeutic effects in treating such a large variety of etiologically and pathogenically diseases. Even if one presumes that the antigenic peptide of which the fusion polypeptide encoded by the claimed polynucleotide is necessarily effective to stimulate an specific

immune response against a particular antigen associated with any given disease (i.e., a type of cancer or an infectious disease caused by a certain pathogen), because it has no particular structure, the claims are directed to antigenic peptides that are defined by their immunogenic properties alone; yet, as explained above, a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability stimulate a specific immune response in a mammal, does not provide an adequate written description of the genus.

To further elaborate upon this issue, Guidelines states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Moreover, because the claims encompass a genus of substances having the ability to stimulate immune responses that must be effective to prevent or treat any number of etiologically and pathologically disparate types of cancer or infectious diseases caused by markedly different pathogens, which otherwise may have very different structures, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described

distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

So, in this case, since the claims are so broad, and the disclosure is so comparably limited, it is submitted that any alleged conception has no more specificity than simply a wish to know the identity of any material with that requisite biological properties, which can be used to make the claimed products and then practice the claimed processes, so as to achieve the claimed prophylactic or therapeutic objectives or effects.

In such instances, the alleged conception fails not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor's idea of the invention. *Burroughs Wellcome Co. v. Barr Laboratories Inc.*, 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994). Reduction to practice in effect provides the only evidence to corroborate conception (and therefore possession) of the invention.

Then, since the claims are not necessarily limited to known materials (i.e., peptides) having the properties of antigenic peptide of which the fusion protein encoded by the claimed polynucleotide is comprised, but rather to such material that might be identified, given the bid set forth in the instant disclosure to do so, it is noted that one cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483 (Bd. Pat. App. & Int. 1993).

With further regard to the inventions of claims directed to processes that necessarily achieve prophylactic or therapeutic effect, or to products intended for use in achieving such effects, it is noted that any given polypeptide may or may not be *immunogenic* in a mammal, as many polypeptides fail to induce an immune response because the mammal's immune response is *tolerant* to the polypeptide. While this concept is further addressed below, it is noted that Khong et al. (*J. Immunol.* 2002 Jan 15; **168** (2): 951-956), for example, teaches that although two peptides consisting of particular fragments of a particular polypeptide (i.e., TRP2-6b) activate cytotoxic T cells *in vitro*, thereby inducing the cells to release a cytokine (i.e., INF-γ), most of the other

peptides consisting of other fragments of the polypeptide, *which were predicted to bind HLA-A2*, only marginally induced such an immune response; see entire document (e.g., page 952, column 1; and page 954, Table VI). This disclosure suggests, despite the ability to predict which peptides are capable of binding MHC class I molecules, the skilled artisan cannot reliably predict which of such peptides are capable of stimulating cytotoxic T cells directed against a tumor associated antigen, such as TRP2-6b or any other antigen associated with a disease.

Furthermore, inasmuch as the claims are directed to a genus of structurally disparate antigenic peptides that are *derived* from tumor associated antigens, for example, it is aptly noted that since their structures may vary substantially many may not elicit an immune response directed against the antigen from which they were originally derived. Then, too, only certain immunogenic fragments might be expected to effectively induce antigen-specific cytotoxic T lymphocytes (CTL) that will kill the cancer cells; other immunogenic fragments will not be effective. This position is supported, for example, by the teachings of Lu et al. (*Cancer Research* 2002; **62**: 5807-5812). Lu et al. teaches that four of five immunogenic fragments of the prostate cancer-associated antigen PSMA were capable of inducing antigen-specific CTL killing of target cells, but only one was effective at recognizing prostate tumor cells expressing the protein; see the entire document (e.g., the abstract). Thus, while some immunogenic fragments of any given tumor-associated antigen may effective to stimulate a CTL-mediated response to the immunogenic fragment, it seems that the artisan cannot predict which immunogenic fragments might be used to elicit an effective anti-tumor immune response, which prevents or suppresses the onset, growth, and/or malignant progression of the disease.

As before noted, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Furthermore, Applicant is again reminded that "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

In this instance, there is no language that adequately describes with the requisite clarity and particularity the genus of claimed antigenic peptides that can be used to construct the fusion polypeptide encoded by the claimed polynucleotide, which can be used to stimulate an immune response in the subject or patient that will be effective to prevent or treat any given type of cancer or infectious disease, so as to achieve the claimed objective or purpose of using the claimed products or of practicing the claimed processes. Once again, a description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

This position is further supported by the numerous references cited in support of the above rejection of the claims under 35 U.S.C. § 101.

Lastly, as noted above, the claims are directed to a plurality of tumor-associated antigens (TAA), which the specification expressly discloses includes "any TAA peptide known or **to be discovered in the future** as periodically published in Cancer Immunity, a Journal of the Academy of Cancer Immunology, at the website http://www.cancerimmunity.org/peptidedatabase/Tcellepitopes.htm [emboldened for emphasis]" (paragraph [0079] of the published application). Since in accordance with the written description requirement set forth under 35 U.S.C. §112, first paragraph, the specification must reasonably convey to the skilled artisan that Applicant had *at the time the application was filed* the claimed subject matter, it is apparent that this requirement cannot be met. The skilled artisan would not conclude that Applicant had at the time the application was filed possession of the claimed invention, which comprises antigenic peptides that have yet to be discovered, identified, or described.

Thus, it is for all of the above reasons that it is submitted that the instant claims, and the disclosure describing the claimed subject matter, fail to satisfy the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Claim Rejections - 35 USC § 102

23. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

24. Claims 1, 3, 11, 12, 23, 24, 26, 29-32, 34, 36, 37, 39, 40, 49, 51, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by WO0101698-A2 (of record).

WO0101698-A2 (Gross et al.) teaches a DNA molecule encoding a chimeric polypeptide comprising a component of a MHC molecule capable of association on a cell surface with an endogenous MHC molecule component of the same class, at a portion of the transmembrane and/or an intracellular region of a signal transduction element capable of activating T cells and, optionally, an antigenic peptide related to an autoimmune disease linked to said chimeric polypeptide by a peptide linker. Gross et al. teaches the MHC component is a monomorphic component, such as the human β2-microglobulin molecule. Gross et al. teaches the human β2-microglobulin molecule is adjoined to the transmembrane and/or intracellular (cytoplasmic) region of a signal transduction element via a bridge peptide. Gross et al. teaches this bridge peptide has a sequence comprised within the membrane-proximal sequence of a class I heavy chain HLA molecule, or more preferably has the sequence that is identical to the instant SEQ ID NO: 1. Gross et al. teaches the chimeric activation receptor of the invention comprises the transmembrane and/or intracellular (cytoplasmic) region of the T-cell receptor CD3, such as the ζ polypeptide. Gross et al. teaches the antigenic peptide is linked to the human β2-microglobulin molecule by a peptide linker. Absent a showing of any difference, it appears that the antigenic peptide related to an autoimmune disease is the same as to the antigenic peptide of which the fusion protein encoded by the claimed polynucleotide, which is "at least one idiotypic peptide expressed by autoreactive T lymphocytes", since, e.g., the insulin B chain peptide used by the prior art is disclosed as the first CD8+ T cell epitope identified as related to an autoimmune

disease; but even so, Gross et al. also teaches the antigenic peptide of which the fusion protein encoded by the claimed polynucleotide is from a viral antigen (i.e., it is comprised of the Ha 255-262 peptide of influenza virus strain A/Japan/305/57). Gross et al. teaches an expression vector comprising the disclosed DNA molecule and cells expressing the fusion polypeptide encoded by the DNA molecule. Gross et al. teaches the vectors are viral vectors.

Double Patenting

25. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

26. Claims 1, 3, 11-13, 26, 29-33, 34, 37, 40, 49, and 52 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 7,319,143-B2. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 1-16 of the patent are directed to a DNA molecule encoding a fusion polypeptide comprising a β2-microglobulin molecule adjoined to a peptide, which in turn is adjoined to a fragment of the human CD3 ζ polypeptide comprising its transmembrane and cytoplasmic domains, wherein the β2-microglobulin molecule is also adjoined to another peptide, which is antigenic and related to an autoimmune disease.

Although the claims of the patent are not expressly directed to an antigenic peptide that comprises a MHC class I epitope of any of a tumor-associated antigen, an antigen from a pathogen, or an idiotypic peptide expressed by autoreactive T cells, the peptide is antigenic and is related to an autoimmune disease.

Accordingly, it seems that the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the patent anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the patent.

27. Claims 1, 3, 11-24, 26, 29-44, 47-53, 56, and 57 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 6-25 of copending Application No. 11/541,566. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed

in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

28. No claim is allowed.

29. The art made of record and not relied upon is considered pertinent to Applicant's disclosure. Lens (*Expert Opin. Biol. Ther.* 2008 Mar; **8** (3): 315-323) reviews the role of vaccine therapy in treating melanoma, disclosing that clinical responses to melanoma vaccines are still poor and that there currently no melanoma vaccine with a proven efficacy. Morris et al. (*Surg. Oncol. Clin. N. Am.* 2007 Oct; **16** (4): 819-831) reviews the limitations of the cancer vaccines. Prehn (*Cancer Cell Int.* 2005 Aug 1; **5** (1): 25) reviews the reasons that cancer vaccines are ineffective. Bradac et al. (*IDrugs*. 2009 Jul; **12** (7): 435-439) reviews the failure of an HIV vaccine to effectively treat AIDS.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

slr
February 26, 2010